Complete Summary

GUIDELINE TITLE

Postmenopausal hormone replacement therapy for the primary prevention of chronic conditions: recommendations and rationale.

BIBLIOGRAPHIC SOURCE(S)

Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale. Ann Intern Med 2002 Nov 19;137(10):834-9. PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Chronic conditions including:

- Cardiovascular disease, including coronary heart disease and stroke
- Thromboembolism
- Breast cancer
- Colon cancer
- Ovarian and endometrial cancer
- Osteoporosis
- Cognition and dementia

Note: The use of hormone replacement therapy (HRT) for treatment of the active symptoms of menopause, such as hot flashes, urogenital symptoms, mood and sleep disturbances, among others, and for the treatment of preexisting conditions are outside the scope of these recommendations.

GUIDELINE CATEGORY

Prevention

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Obstetrics and Gynecology
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To summarize the current U.S. Preventive Services Task Force (USPSTF) recommendations for use of hormone replacement therapy (HRT) for the primary prevention of chronic conditions in postmenopausal women
- To update the 1996 recommendations contained in the Guide to Clinical Preventive Services, second edition

TARGET POPULATION

Postmenopausal women

INTERVENTIONS AND PRACTICES CONSIDERED

Hormone replacement therapy (HRT)

MAJOR OUTCOMES CONSIDERED

The use of postmenopausal hormone replacement therapy (HRT) and:

- Cardiovascular disease (CVD), coronary heart disease (CHD), and stroke incidence and/or mortality
- Risk of venous thromboembolism, including deep venous thrombosis (DVT), pulmonary embolism, or both
- Bone mineral density (BMD) and risk of fracture
- Cognitive function, including memory, attention, concept formation and reasoning, motor speed, mental status, and verbal functions and language
- Breast cancer incidence, mortality, or both
- Risk of colon, endometrial and ovarian cancer
- Risk of cholecystitis

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): Systematic evidence reviews were prepared by the Oregon Health & Science University, Evidence-based Practice Center (EPC) for the Agency for Healthcare Research and Quality (AHRQ) for use by the U.S. Preventive Services Task Force (USPSTF) (see documents listed below and in the "Companion Documents" field).

Literature Search Strategy

Methods of searching the literature, selecting abstracts, reviewing, abstracting, and rating studies, and conducting meta-analyses were standardized for all topics. Because the literature for each topic varied, each review was also subject to topic-specific modifications in methods. Detailed methods for each topic are presented in each individual systematic evidence review (see below).

In conjunction with a medical librarian, topic-specific searches were conducted using MEDLINE (1966-2001), HealthSTAR (1975-2001), and the Cochrane Controlled Trials Register; dates of searches varied with some topics. Additional articles were obtained by consulting experts and by reviewing reference lists of pertinent studies, reviews, and editorials. Only published data in meta-analyses were used.

Inclusion/Exclusion Criteria

Inclusion and exclusion criteria were developed by the investigators for each topic. In general, studies were included if they contained a comparison group of hormone replacement therapy (HRT) nonusers and reported data relating to HRT use and clinical outcomes of interest. Studies were excluded if the population was selected according to prior events or presence of conditions associated with higher risks for targeted outcomes. Hormone replacement therapy use was classified as unopposed estrogen replacement (estrogen only) or combined (estrogen plus progestin) when specified. When data were available, effects of formulation, dose, and duration were reported. In studies with multiple publications from the same cohort or population, only data from the most recent publication were included in the meta-analyses. Adjusted statistics were used when reported.

In addition to the systematic literature review, two recently published randomized controlled trials (RCTs) with pertinent findings were included. The Women's Health Initiative (WHI), a primary prevention trial, reported results of 16,608 healthy postmenopausal women after 5.2 years of daily combined HRT or placebo. Also cited are the noncardiac outcomes of the Heart and Estrogen/Progestin

Replacement Study Follow-up (HERS II), a trial of daily combined HRT in 2,321 postmenopausal women with preexisting coronary heart disease after 6.8 years.

Individual Evidence Reviews

- Nelson H, Humphrey L, LeBlanc E, et al. Postmenopausal hormone replacement therapy for the primary prevention of chronic conditions: a summary of the evidence. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. Electronic copies available from the Agency for Healthcare Research and Quality (AHRQ) Web site.
- Humphrey LL, Takano L, and Chan BKS. Postmenopausal hormone replacement therapy and cardiovascular disease. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Sep. (Systematic evidence review; no. 10). Electronic copies available from the AHRQ Web site.
- Miller J, Chan BKS, Nelson HD. Hormone replacement therapy and risk of venous thromboembolism. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. (Systematic evidence review; no. 11). Electronic copies available from the AHRQ Web site. Also available from the National Library of Medicine Health Services/Technology Assessment Text (HSTAT) database.
- Nelson HD. Hormone replacement therapy and osteoporosis. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. (Systematic evidence review; no. 12). Electronic copies available from the AHRQ Web site.
- LeBlanc E, Chan B, Nelson H. Hormone replacement therapy and cognition. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. (Systematic evidence review; no. 13). Electronic copies available from the AHRQ Web site. Also available from the National Library of Medicine HSTAT database.
- Humphrey LL, Chan BKS. Postmenopausal hormone replacement therapy and breast cancer. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. (Systematic evidence review; no. 14). Electronic copies available from the AHRQ Web site.

NUMBER OF SOURCE DOCUMENTS

Cardiovascular Disease

A total of 1,926 abstracts were identified and reviewed: 1,668 in the cardiovascular disease (CVD) search and 258 in the stroke search. Sixty-five studies about hormone replacement therapy (HRT) and cardiovascular disease met criteria for full text review.

- Coronary artery disease (CAD) and HRT: 34 cohort studies, 24 case-control studies, 4 angiography studies of secondary prevention of (CAD), 2 randomized controlled trials of secondary prevention of CAD with HRT, and preliminary findings from the Women's Health Initiative.
- Stroke and HRT: 24 cohort and 8 case-control studies describing stroke and HRT.

Thromboembolism

A total of 3,363 abstracts were identified from the search of postmenopausal HRT and venous thromboembolism. Twelve abstracts (3 randomized controlled trials[RCTs], 8 case-control studies, and 1 cohort study) met inclusion criteria and contained primary data.

Breast Cancer

The total number is not stated; 38 documents met inclusion criteria, including 8 meta-analyses from the years 1988-1997, 1 nested case-control study, 14 case-control studies, and 15 cohort studies.

Cognition

A total of 509 abstracts were identified. From the original search, 56 articles with primary data on the relationship between HRT and cognition in postmenopausal women without dementia were then identified. An additional 16 articles with primary data were identified from reference lists of relevant review.

Osteoporosis

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence on a 3-point scale (good, fair, or poor).

Good

Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair

Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of evidence on health outcomes.

Poor

Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Note: See the companion document titled "Current Methods of the U.S. Preventive Services Task Force: a Review of the Process" (Am J Prev Med 2001 Apr;20[3S]:21-35) for a more detailed description of the methods used to assess the quality and strength of the evidence for the three strata at which the evidence was reviewed.

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Meta-Analysis of Observational Trials
Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): Systematic evidence reviews were prepared by the Oregon Health Sciences University, Evidence-based Practice Center (EPC) for the Agency for Healthcare Research and Quality (AHRQ) for use by the U.S. Preventive Services Task Force. These documents explain the specific data extraction and synthesis for each condition (see documents listed below and in the "Companion Documents" field).

Data Extraction and Synthesis

Meta-analyses were conducted for some of the topics because either previous meta-analyses had not been published, or they were outdated or inadequate. Adjusted relative risk (RR) estimates were used when available or were calculated when possible. Under the modeling assumptions made by each study, the logarithm of the relative risk (logRR) had a normal distribution. Standard errors (SEs) for logRR were calculated from reported confidence intervals (CIs) or P values. The logRR and standard errors provided the data points for the meta-analyses. Heterogeneity was assessed with study-level stratification factors in the regression models. Fixed and random-effects models were fit on the data by using the Bayesian data analytic framework. Only the random-effects model is reported because the results of the two models were similar in all cases. Inference on the parameters was done via posterior probability distributions. The data were analyzed with WinBUGS software, which uses a method of Markov chain Monte Carlo called Gibbs sampling to simulate posterior probability distributions.

Sensitivity analysis was performed with different prior distributions, combining only studies with similar methods and excluding poor-quality studies and those with important biases or limitations. Sensitivity analysis varied according to the needs of each meta-analysis.

Also evaluated were studies for selection bias by using funnel plots, and also investigated was the sensitivity of the analysis to studies possibly missed because of publication bias by trim and fill. Results were unaffected, although this technique does not entirely rule out potential publication bias.

Individual Evidence Reviews

- Nelson H, Humphrey L, LeBlanc E, et al. Postmenopausal hormone replacement therapy for the primary prevention of chronic conditions: a summary of the evidence. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. Electronic copies available from the Agency for Healthcare Research and Quality (AHRQ) Web site.
- Humphrey LL, Takano L, and Chan BKS. Postmenopausal hormone replacement therapy and cardiovascular disease. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Sep. (Systematic evidence review; no. 10). Electronic copies available from the AHRQ Web site.
- Miller J, Chan BKS, Nelson HD. Hormone replacement therapy and risk of venous thromboembolism. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. (Systematic evidence review; no. 11). Electronic copies available from the AHRQ Web site. Also available from the National Library of Medicine Health Services/Technology Assessment Text (HSTAT) database.
- Nelson HD. Hormone replacement therapy and osteoporosis. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. (Systematic evidence review; no. 12). Electronic copies available from the AHRQ Web site.
- LeBlanc E, Chan B, Nelson H. Hormone replacement therapy and cognition. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. (Systematic evidence review; no. 13). Electronic copies available from the AHRQ Web site. Also available from the National Library of Medicine HSTAT database.
- Humphrey LL, Chan BKS. Postmenopausal hormone replacement therapy and breast cancer. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. (Systematic evidence review; no. 14). Electronic copies available from the AHRQ Web site.
- Humphrey LL, Chan BK, Sox HC. Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease. Ann Intern Med. 2002 Aug 20;137(4):273-84. Electronic copies available from the AHRQ Web site. Also available from the Annals of Internal Medicine Online.
- Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2002 May 7;136(9):680-90. Electronic copies available from the Annals of Internal Medicine Online.
- LeBlanc E, Janowsky J, Chan B, Nelson H. Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 2001 Mar 21;285(11):1489-99.
- Nelson H, Humphrey L, Nygren P, Teutsch S, Allan J. Postmenopausal hormone replacement therapy: scientific review. JAMA 2002 Aug 21;288(7):872-81.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Balance Sheets
Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

When the overall quality of the evidence is judged to be good or fair, the U.S. Preventive Services Task Force (USPSTF) proceeds to consider the magnitude of net benefit to be expected from implementation of the preventive service. Determining net benefit requires assessing both the magnitude of benefits and the magnitude of harms and weighing the two.

The USPSTF classifies benefits, harms, and net benefits on a 4-point scale: "substantial," "moderate," "small," and "zero/negative."

"Outcomes tables" (similar to 'balance sheets') are the USPSTF's standard resource for estimating the magnitude of benefit. These tables, prepared by the topic teams for use at USPSTF meetings, compare the condition specific outcomes expected for a hypothetical primary care population with and without use of the preventive service. These comparisons may be extended to consider only people of specified age or risk groups or other aspects of implementation. Thus, outcomes tables allow the USPSTF to examine directly how the preventive services affects benefits for various groups.

When evidence on harms is available, the topic teams assess its quality in a manner like that for benefits and include adverse events in the outcomes tables. When few harms data are available, the USPSTF does not assume that harms are small or nonexistent. It recognizes a responsibility to consider which harms are likely and judge their potential frequency and the severity that might ensue from implementing the service. It uses whatever evidence exists to construct a general confidence interval on the 4-point scale (e.g., substantial, moderate, small, and zero/negative).

Value judgments are involved in using the information in an outcomes table to rate either benefits or harms on the USPSTF's 4-point scale. Value judgments are also needed to weigh benefits against harms to arrive a rating of net benefit.

In making its determinations of net benefit, the USPSTF strives to consider what it believes are the general values of most people. It does this with greater confidence for certain outcomes (e.g., death) about which there is little disagreement about undesirability, but it recognizes that the degree of risk people are willing to accept to avert other outcomes (e.g., cataracts) can vary considerably. When the USPSTF perceives that preferences among individuals vary greatly, and that these variations are sufficient to make trade-off of benefits and harms a 'close-call', then it will often assign a C recommendation (see the "Recommendation Rating Scheme" field). This recommendation indicates the decision is likely to be sensitive to individual patient preferences.

The USPSTF uses its assessment of the evidence and magnitude of net benefit to make recommendations. The general principles the USPSTF follows in making recommendations are outlined in Table 5 of the companion document cited below. The USPSTF liaisons on the topic team compose the first drafts of the recommendations and rationale statements, which the full panel then reviews and edits. Recommendations are based on formal voting procedures that include explicit rules for determining the views of the majority.

From: Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow, CD, Teutsch SM, Atkins D. Current methods of the U.S. Preventive Services Task Force: a review of the

process. Methods Work Group, Third U.S. Preventive Services Task Force. Am J Prev Med 2001 Apr;20(3S):21-35.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, or I), reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

A

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians provide [the service] to eligible patients. (The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.)

B

The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians provide [the service] to eligible patients. (The USPSTF found at least fair evidence that [the service] improves health outcomes and concludes that benefits outweigh harms.)

C

The U.S. Preventive Services Task Force (USPSTF) makes no recommendation for or against routine provision of [the service]. (The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms it too close to justify a general recommendation.)

D

The U.S. Preventive Services Task Force (USPSTF) recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.)

I

The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Peer Review. Before the U.S. Preventive Services Task Force makes its final determinations about recommendations on a given preventive service, the Evidence-based Practice Center and the Agency for Healthcare Research and Quality send a draft systematic evidence review to 4 to 6 external experts and to federal agencies and professional and disease-based health organizations with interests in the topic. They ask the experts to examine the review critically for accuracy and completeness and to respond to a series of specific questions about the document. After assembling these external review comments and documenting the proposed response to key comments, the topic team presents this information to the Task Force in memo form. In this way, the Task Force can consider these external comments and a final version of the systematic review before it votes on its recommendations about the service. Draft recommendations are then circulated for comment from reviewers representing professional societies, voluntary organizations and Federal agencies. These comments are discussed before the whole U.S. Preventive Services Task Force before final recommendations are confirmed.

Recommendations of Others. Recommendations for postmenopausal hormone replacement therapy from the following groups were discussed: the American Academy of Family Physicians (AAFP), the American Association of Clinical Endocrinologists (AACE), the American College of Obstetricians and Gynecologists (ACOG), the American College of Preventive Medicine (ACPM), the American Heart Association (AHA), the Canadian Task Force on Preventive Health Care (CTFPHC), and the North American Menopause Society (NAMS).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The U.S. Preventive Services Task Force grades its recommendations (A, B, C, D, or I) and the quality of the overall evidence for a service (good, fair, poor). The definitions of these grades can be found at the end of the "Major Recommendations" field.

The U.S. Preventive Services Task Force (USPSTF) recommends against the routine use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women. D recommendation.

The USPSTF found fair to good evidence that the combination of estrogen and progestin has both benefits and harms. Benefits include increased bone mineral density (good evidence), reduced risk for fracture (fair to good evidence), and reduced risk for colorectal cancer (fair evidence). Harms include increased risk for breast cancer (good evidence), venous thromboembolism (good evidence), coronary heart disease (CHD) (fair to good evidence), stroke (fair evidence) and cholecystitis (fair evidence). Evidence was insufficient to assess the effects of hormone replacement therapy (HRT) on other important outcomes, such as

dementia and cognitive function, ovarian cancer, mortality from breast cancer or cardiovascular disease, or all-cause mortality.

The USPSTF concluded that the harmful effects of estrogen and progestin are likely to exceed the chronic disease prevention benefits in most women. The USPSTF did not evaluate the use of HRT to treat symptoms of menopause, such as vasomotor symptoms (hot flashes) or urogenital symptoms. The balance of benefits and harms for an individual woman will be influenced by her personal preferences, individual risks for specific chronic diseases, and the presence of menopausal symptoms.

The USPSTF concludes that the evidence is insufficient to recommend for or against the use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. I recommendation.

The USPSTF found fair to good evidence that the use of unopposed estrogen has both benefits and harms. Although most current data come from observational studies, likely benefits include increased bone mineral density, reduced fracture risk, and reduced risk for colorectal cancer. Likely harms include increased risk for venous thromboembolism, cholecystitis, and stroke; in women who have not had a hysterectomy, unopposed estrogen increases the risk for endometrial cancer. Evidence is insufficient to determine the effects of unopposed estrogen on the risk for breast and ovarian cancer, CHD, dementia and cognitive function, or mortality. As a result, the USPSTF could not determine whether the benefits of unopposed estrogen outweigh the harms for women who have had a hysterectomy. Better data on benefits and harms are expected from ongoing randomized trials, including the Women´s Health Initiative (WHI) study of unopposed estrogen in women who have had a hysterectomy.

Clinical Considerations

- Although the USPSTF concludes that the harms of estrogen-progestin therapy are likely to outweigh the chronic disease prevention benefits for most women, the absolute increase in risk from HRT is modest. Some women, depending on their risk characteristics and personal preferences, might decide that the benefits of taking HRT outweigh the potential harms. Based on results reported from the WHI study for women aged 50 to 79 years (average age 63 years), 10,000 women taking estrogen and progestin for 1 year might experience 7 additional CHD events, 8 more strokes, 8 more pulmonary emboli, and 8 more invasive breast cancers, but would also have 6 fewer cases of colorectal cancer and 5 fewer hip fractures.
- Clinicians should develop a shared decision-making approach to preventing chronic diseases in perimenopausal and postmenopausal women. This approach should consider individual risk factors and preferences in selecting effective interventions for reducing the risks for fracture, heart disease, and cancer. Clinicians should discuss with patients other effective strategies for preventing osteoporosis and fractures (see other USPSTF recommendations available on the USPSTF Web site: Screening for Postmenopausal Osteoporosis, Screening for Hypertension, Screening Adults for Lipid Disorders, Counseling to Prevent Tobacco Use, Counseling to Promote a Healthy Diet, Counseling to Promote Physical Activity, Screening for Breast Cancer, and Screening for Colorectal Cancer).

- The USPSTF did not consider the use of HRT for the management of menopausal symptoms. Decisions to initiate or continue HRT for menopausal symptoms should be made on the basis of discussions between a woman and her clinician. Women should be informed that there are some risks (such as the risk for venous thromboembolism, coronary heart disease, and stroke) within the first 1 to 2 years of therapy, whereas other risks (such as the risk for breast cancer) appear to increase with longer-term HRT. Other expert groups have recommended that women who decide to take HRT for the relief of menopausal symptoms use the lowest effective dose for the shortest possible time.
- The quality of evidence on the benefits and harms of HRT varies for different hormone regimens. Other than the two large randomized controlled trials of daily conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA), most of the evidence on HRT comes from observational studies that did not differentiate among the effects of specific hormone preparations. Until data indicate that other HRT regimens have a favorable balance of benefits to harms, a cautious approach would be to avoid using HRT routinely for the specific purpose of preventing chronic disease in women.
- Evidence is inconclusive to determine whether phytoestrogens (isoflavones such as iproflavone, which are found in soy milk, soy flour, tofu, and other soy products) are effective for reducing the risk for osteoporosis or cardiovascular disease.

Definitions:

The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, or I), reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

A

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians provide [the service] to eligible patients. (The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.)

B

The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians provide [the service] to eligible patients. (The USPSTF found at least fair evidence that [the service] improves health outcomes and concludes that benefits outweigh harms.)

C

The U.S. Preventive Services Task Force (USPSTF) makes no recommendation for or against routine provision of [the service]. (The US Preventive Services Task Force found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms it too close to justify a general recommendation.)

D

The U.S. Preventive Services Task Force (USPSTF) recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.)

I

The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)

The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a 3-point scale (good, fair, or poor).

Good

Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair

Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of evidence on health outcomes.

Poor

Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting each recommendation is identified in the "Major Recommendations" field.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Osteoporosis and Fractures

Low bone density is associated with an increased risk for osteoporotic fractures. Good evidence from observational studies and randomized clinical trials demonstrate that estrogen therapy increases bone density and reduces risk for fractures. Good evidence from many randomized clinical trials has demonstrated that hormone replacement therapy (HRT) increases bone density at the hip, the lumbar spine, and peripheral sites. A meta-analysis of 22 trials of estrogen reported an overall 27% reduction in nonvertebral fractures (relative risk [RR], 0.73; 95% confidence interval [CI], 0.56 to 0.94), although the quality of individual studies varied. Observational studies have also demonstrated reductions in fractures of the vertebrae (RR for ever use, 0.6; 95% CI, 0.36 to 0.99), wrist (RR for current use, 0.39; 95% CI, 0.24 to 0.64), and possibly hip (RR for current use, 0.64; 95% CI, 0.32 to 1.04) among women taking HRT. The Heart and Estrogen/Progestin Replacement Study (HERS and its unblinded follow-up study, HERS II), a trial of combined estrogen and progestin (conjugated equine estrogen [CEE] and medroxyprogesterone acetate [MPA]) for the secondary prevention of heart disease that reported many other outcomes, found no reduction in hip, wrist, vertebral, or total fractures with hormone therapy (relative hazard [RH] for total fractures, 1.04; 95% CI, 0.87 to 1.25). The Women´s Health Initiative (WHI) found significant reductions in total fracture risk (RH, 0.76; 95% CI, 0.63 to 0.92) among healthy women taking estrogen and progestin. The WHI also reported reductions for hip (RH, 0.66; 95% CI, 0.33 to 1.33) and vertebral fracture (RH, 0.66; 95% CI, 0.32 to 1.34), although these did not achieve statistical significance in adjusted analyses. The WHI reported both nominal and adjusted confidence intervals. The U.S. Preventive Services Task Force (USPSTF) relied on nominal confidence intervals for the primary outcomes of breast cancer and coronary heart disease (CHD) and adjusted confidence intervals for other secondary outcomes. The USPSTF concluded that there was good evidence that HRT increases bone mineral density and fair to good evidence that it reduces fractures.

Colorectal Cancer

A meta-analysis of 18 observational studies of postmenopausal women reported a 20% reduction in cancer of the colon (RR, 0.80; 95% CI, 0.74 to 0.86) and a 19% reduction in cancer of the rectum (RR, 0.81; 95% CI, 0.72 to 0.92) among women who had ever used HRT. This decrease in risk was more apparent when current users were compared with those who had never used HRT (RR, 0.66; 95% CI, 0.59 to 0.74). Comparable results from the WHI study were reported for women taking conjugated equine estrogen and medroxyprogestrone acetate (RH, 0.63; 95% CI, 0.32 to 1.24), and the HERS studies also found reduced incidence of colon cancer (RH, 0.8; 95% CI, 0.46 to 1.45). The USPSTF concluded that there was fair evidence that HRT reduces colorectal cancer incidence.

POTENTIAL HARMS

Breast Cancer

Because breast tissue is sensitive to reproductive hormones, there has been long-standing concern about breast cancer risk among women who take hormone replacement therapy (HRT). The estrogen and progestin arm of the Women's

Health Initiative (WHI) study was recently terminated because of an increased breast cancer incidence (relative hazard [RH], 1.26; 95% confidence interval [CI], 1.00 to 1.59). However, no effect on breast cancer mortality was observed. Comparable increases in breast cancer incidence were observed among women taking estrogen and progestin over 6.8 years of follow-up in the Heart and Estrogen/Progestin Replacement Studies (HERS) (RH, 1.27; 95% CI, 0.84 to 1.94). Although many good observational studies on breast cancer and meta-analyses of these studies have been conducted, the conclusions are limited by healthy-user bias; variations in specific preparations, dose, and duration of estrogen and progestin therapy; and differences in the ways in which breast cancer end points were ascertained. In the aggregate, breast cancer incidence is slightly increased for current (RR, 1.21 to 1.40) or long-term (>5 years) users (RR, 1.23 to 1.35) compared with nonusers. However, there seems to be no effect on or decreased breast cancer mortality in ever- or short-term users (RR, 0.5 to 1.0). The effects of long-term HRT use on breast cancer mortality in two good-quality cohort studies are conflicting. Whether the combination of estrogen and progestin confers a greater risk than estrogen alone is unknown; WHI investigators have reported that no increase in breast cancer has been observed after 5 years of follow-up in the ongoing study of unopposed estrogen in women who have had a hysterectomy. The U.S. Preventive Services Task Force (USPSTF) concluded that there was fair to good evidence that HRT increases the incidence, of breast cancer (with best evidence for estrogen plus progestin), but its effects on breast cancer mortality are uncertain.

Coronary Heart Disease

Coronary heart disease (CHD) remains the leading cause of death among women. Hormone replacement therapy (HRT) has diverse effects on lipid levels, endothelial wall function, blood pressure, coagulation factors, weight, and inflammation (for example, C-reactive protein). In the WHI study, women who took conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) daily had an increased risk for CHD (fatal and non-fatal myocardial infarctions), which was evident shortly after initiation of the study (RH, 1.29; 95% CI, 1.02 to 1.63). Coronary heart disease mortality was not significantly increased (RH, 1.18; 95% CI, 0.70 to 1.97). Meta-analysis of observational studies showed a statistically significant reduction in CHD (RR, 0.80; 95% CI, 0.68 to 0.95) among current HRT users, but not among ever or past users, compared with women who had never taken HRT (nonusers). However, among studies that controlled for socioeconomic status (social class, education, or income), no benefit was seen among current HRT users (RH, 0.97; 95% CI, 0.82 to 1.16), suggesting that the observed difference may be due to confounding by socioeconomic status and other lifestyle factors (e.g., exercise, alcohol use) rather than use of HRT. Coronary heart disease mortality in observational studies is reduced among current HRT users (RR, 0.62; 95% CI, 0.40 to 0.90) but is not reduced among ever, past, or all users. Thus, selection bias (the tendency of healthier women to use HRT) appears to explain the apparent protective effect of estrogen on CHD seen in observational studies. The USPSTF concluded that HRT does not decrease, and may in fact increase, the incidence of CHD. The effects of HRT on CHD mortality, however, are less certain.

Stroke

A meta-analysis of 9 observational primary prevention studies suggests that HRT use is associated with a small increase in stroke incidence (RR, 1.12; 95% CI, 1.01 to 1.23), due primarily to an increase in thromboembolic stroke (RR, 1.20; 95% CI, 1.01 to 1.40). The risk for subarachnoid bleeding and hemorrhagic stroke was not increased, and the overall stroke mortality was marginally reduced (RR, 0.81; 95% CI, 0.71 to 0.92). These results are consistent with findings from the estrogen and progestin arm of the Women's Health Initiative (WHI) study, which reported increased incidence of stroke in women taking CEE/MPA daily (RH, 1.41; 95% CI, 0.86 to 2.31). Two secondary prevention trials that were not included in the USPSTF review of HRT for primary prevention, reported no clear effect of HRT on stroke incidence, but stroke mortality was increased in women with a previous stroke. The USPSTF concluded that there is fair evidence that HRT increases the risk for stroke.

Venous Thromboembolism (Deep Venous Thrombosis and Pulmonary Embolism)

In a meta-analysis of 12 studies (3 randomized, controlled trials; 8 case-control studies; and 1 cohort study), HRT was associated with an increased risk for venous thromboembolism (RR, 2.14; 95% CI, 1.64 to 2.81). Five of six studies that examined the effects of HRT over time reported that the risk was highest within the first year of use (RR, 3.49; 95% CI, 2.33 to 5.59). These results are consistent with the findings in the estrogen and progestin arm of the WHI, which reported a 2-fold increased rate of venous thromboembolic (VTE) disease (RH, 2.11; 95% CI, 1.26 to 3.55), including deep venous thrombosis (DVT) and pulmonary embolism (PE), in women taking CEE/MPA daily. The USPSTF concluded that there is good evidence that HRT increases the risk for venous thromboembolism.

Endometrial and Ovarian Cancer

Results of a previously published meta-analysis of 29 good-quality observational studies of endometrial cancer reported a relative risk (RR) of 2.3 (95% CI, 2.1 to 2.5) for users of unopposed estrogen compared with nonusers. Risks increased with increasing duration of use (RR, 9.5 for >10 years of use). The risk for endometrial cancer remained elevated 5 or more years after discontinuation of unopposed estrogen therapy in these studies. With combined estrogen-progestin regimens, cohort studies showed a decreased risk for endometrial cancer (RR, 0.4; 95% CI, 0.2 to 0.6) compared with nonusers, but case-control studies showed an increase in risk (odds ratio [OR], 1.8; 95% CI, 1.1 to 3.1). Estrogen and progestin did not increase the risk for endometrial cancer in HERS (RH, 0.25; 95% CI, 0.05 to 1.18) or in the WHI (RH, 0.83; 95% CI, 0.29 to 2.32). The USPSTF concluded that unopposed estrogen, but not combined estrogen-progestin therapy, increases risk for endometrial cancer.

Data on the association between the use of HRT and the risk for ovarian cancer are inconsistent. Results of case-control studies have been mixed, but two good-quality cohort studies reported increased risks (RR, 1.8 to 2.2) for ovarian cancer or ovarian cancer mortality among women who had taken HRT for 10 years or more; a third study found no effect of HRT on ovarian cancer mortality. One study suggested higher risk with unopposed estrogen than with estrogen-progestin therapy, but data are insufficient to resolve the effects of different formulations or

doses of HRT on ovarian cancer risk. Neither the WHI nor HERS has reported risk for ovarian cancer. The USPSTF concluded that evidence was insufficient to determine the effect of HRT on ovarian cancer.

Cholecystitis

Many but not all studies have reported an association between HRT and gallbladder disease. Results from a good-quality cohort study, the Nurses´ Health Study, reported an increase in risk for cholecystitis among current HRT users (RR, 1.8; 95% CI, 1.6 to 2.0) and long-term users (>5 years) (RR, 2.5; 95% CI, 2.0 to 2.9) compared with nonusers. Risk for cholecystitis remained elevated among past users. An increase in biliary tract surgery during 6.8 years of follow-up was reported among women taking estrogen plus progestin compared with those taking placebo (RR, 1.48; 95% CI, 1.12 to 1.95) in HERS; the WHI has not reported biliary tract outcomes. The USPSTF concluded that there is fair evidence that HRT increases the risk for cholecystitis.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Uncertain Benefits or Harms of Hormone Replacement Therapy

Cognition and Dementia

Nine randomized controlled trials examining the effect of hormone replacement therapy (HRT) on cognition showed improvement in verbal memory, vigilance, reasoning, and motor speed among women who had menopausal symptoms but not among women who were asymptomatic at baseline. Because of heterogeneity and variation in assessment of outcomes among studies, meta-analysis of these studies was not performed for the U.S. Preventive Services Task Force (USPSTF). A meta-analysis of 12 observational studies (1 of good quality, 3 of fair quality, and 8 of poor quality) showed a reduction in the risk for dementia among postmenopausal women taking HRT (relative reisk [RR], 0.66; 95% confidence interval [CI], 0.53 to 0.82). Neither the Women's Health Initiative (WHI) nor the Heart and Estrogen/Progestin Replacement Study (HERS) has yet reported effects of HRT on cognition and dementia, but other ongoing trials are examining the effects of HRT on these endpoints. Given the methodologic limitations of the available studies and the potential for confounding or selection bias, the USPSTF concluded that there is insufficient evidence to determine whether HRT reduces the risk for dementia or cognitive dysfunction in otherwise healthy women.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The experiences of the first and second U.S. Preventive Services Task Force (USPSTF), as well as that of other evidence-based guideline efforts, have highlighted the importance of identifying effective ways to implement clinical recommendations. Practice guidelines are relatively weak tools for changing

clinical practice when used in isolation. To effect change, guidelines must be coupled with strategies to improve their acceptance and feasibility. Such strategies include enlisting the support of local opinion leaders, using reminder systems for clinicians and patients, adopting standing orders, and audit and feedback of information to clinicians about their compliance with recommended practice.

In the case of preventive services guidelines, implementation needs to go beyond traditional dissemination and promotion efforts to recognize the added patient and clinician barriers that affect preventive care. These include clinicians' ambivalence about whether preventive medicine is part of their job, the psychological and practical challenges that patients face in changing behaviors, lack of access to health care or of insurance coverage for preventive services for some patients, competing pressures within the context of shorter office visits, and the lack of organized systems in most practices to ensure the delivery of recommended preventive care.

Neither the resources nor the composition of the U.S. Preventive Services Task Force equip it to address these numerous implementation challenges, but a number of related efforts seek to increase the impact of future U.S. Preventive Services Task Force reports. The U.S. Preventive Services Task Force convened representatives from the various audiences for the Guide "Put Prevention Into Practice. A Step-by-Step Guide to Delivering Clinical Preventive Services: A Systems Approach" - clinicians, consumers and policy makers from health plans, national organizations and Congressional staff - about how to modify the content and format of its products to address their needs. With funding from the Robert Wood Johnson Foundation, the U.S. Preventive Services Task Force and Community Guide effort have conducted an audience analysis to further explore implementation needs. The Put Prevention into Practice initiative at the Agency for Healthcare Research and Quality (AHRQ) has developed office tools such as patient booklets, posters, and handheld patient mini-records, and a new implementation guide for state health departments.

Dissemination strategies have changed dramatically in this age of electronic information. While recognizing the continuing value of journals and other print formats for dissemination, the Agency for Healthcare Research and Quality will make all U.S. Preventive Services Task Force (USPSTF) products available through its Web site. The combination of electronic access and extensive material in the public domain should make it easier for a broad audience of users to access U.S. Preventive Services Task Force materials and adapt them for their local needs. Online access to U.S. Preventive Services Task Force products also opens up new possibilities for the appearance of the third edition of the Guide to Clinical Preventive Services. Freed from having to serve as primary repository for all of U.S. Preventive Services Task Force work, the next Guide may be much slimmer than the almost 1000 pages of the second edition.

To be successful, approaches for implementing prevention have to be tailored to the local level and deal with the specific barriers at a given site, typically requiring the redesign of systems of care. Such a systems approach to prevention has had notable success in established staff-model health maintenance organizations, by addressing organization of care, emphasizing a philosophy of prevention, and altering the training and incentives for clinicians. Staff-model plans also benefit

from integrated information systems that can track the use of needed services and generate automatic reminders aimed at patients and clinicians, some of the most consistently successful interventions. Information systems remain a major challenge for individual clinicians' offices, however, as well as for looser affiliations of practices in network-model managed care and independent practice associations, where data on patient visits, referrals and test results are not always centralized.

RELATED QUALITY TOOLS

- Pocket Guide to Good Health for Adults

- A Step-by-Step Guide to Delivering Clinical Preventive Services: A Systems Approach

- Postmenopausal Hormone Replacement Therapy for Primary Prevention of Chronic Conditions. What's New from the USPSTF.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale. Ann Intern Med 2002 Nov 19;137(10):834-9. PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 (revised 2002)

GUIDELINE DEVELOPER(S)

United States Preventive Services Task Force - Independent Expert Panel

GUIDELINE DEVELOPER COMMENT

The U.S. Preventive Services Task Force (USPSTF) is a Federally-appointed panel of independent experts. Conclusions of the USPSTF do not necessarily reflect policy of the U.S. Department of Health and Human Services (DHHS) or DHHS agencies.

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GUIDELINE COMMITTEE

U.S. Preventive Services Task Force (USPSTF)

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The U.S. Preventive Services Task force has an explicit policy concerning conflict of interest. All members and evidence-based practice center (EPC) staff disclose at each meeting if they have an important financial conflict for each topic being discussed. Task Force members and EPC staff with conflicts can participate in discussions about evidence, but members abstain from voting on recommendations about the topic in question.

From: Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow, CD, Teutsch SM, Atkins D. Current methods of the U.S. Preventive Services Task Force: a review of the process. Methods Work Group, Third U.S. Preventive Services Task Force. Am J Prev Med 2001 Apr;20(3S):21-35.

GUIDELINE STATUS

This is the current release of the guideline.

This release updates a previously published guideline: U.S. Preventive Services Task Force. Postmenopausal hormone prophylaxis. In: Guide to clinical preventive services. 2nd ed. Baltimore (MD): Williams & Wilkins; 1996.

GUIDELINE AVAILABILITY

Electronic copies: Available from the U.S. Preventive Services Task Force (USPSTF) Web site. Also available from the Annals of Internal Medicine Online and the National Library of Medicine's Health Services/Technology Assessment Text (HSTAT) Web site.

Print copies: Available from the Agency for Healthcare Research and Quality (AHRQ) Publications Clearinghouse. For more information, go to http://www.ahrq.gov/news/pubsix.htm or call 1-800-358-9295 (U.S. only).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

Evidence Reviews:

- Nelson H, Humphrey L, LeBlanc E, et al. Postmenopausal hormone replacement therapy for the primary prevention of chronic conditions: a summary of the evidence. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. Electronic copies available from the Agency for Healthcare Research and Quality (AHRQ) Web site.
- Humphrey LL, Takano L, and Chan BKS. Postmenopausal hormone replacement therapy and cardiovascular disease. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Sep. (Systematic evidence review; no. 10). Electronic copies available from the AHRQ Web site.
- Miller J, Chan BKS, Nelson HD. Hormone replacement therapy and risk of venous thromboembolism. Rockville (MD); Agency for Healthcare Research and Quality; 2002 Aug. (Systematic evidence review; no. 11). Electronic copies available from the AHRQ Web site. Also available from the National Library of Medicine Health Services/Technology Assessment Text (HSTAT) database.
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- Woolf SH, Atkins D. The evolving role of prevention in health care: contributions of the U.S. Preventive Services Task Force. Am J Prev Med 2001 Apr;20(3S):13-20.
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- Saha S, Hoerger TJ, Pignone MP, Teutsch SM, Helfand M, Mandelblatt. The art and science of incorporating cost effectiveness into evidence-based recommendations for clinical preventive services. Cost Work Group of the Third U.S. Preventive Services Task Force. Am J Prev Med 2001 Apr;20(3S):36-43.

Electronic copies: Available from U.S. Preventive Services Task Force (USPSTF) Web site.

Additional Implementation Tools:

- A step-by-step guide to delivering clinical preventive services: a systems approach. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ), 2001. 189 p. (Pub. No. APPIP01-0001). Electronic copies available from the AHRQ Web site.

  Print copies: Available from the Agency for Healthcare Research and Quality Publications Clearinghouse. For more information, go to http://www.ahrq.gov/news/pubsix.htm or call 1-800-358-9295 (U.S. only).

- The Preventive Services Selector, an application for Palm Pilots and other PDA's, is also available from the AHRQ Web site.
- Postmenopausal hormone replacement therapy for primary prevention of chronic conditions. What's new from the USPSTF?. Rockville (MD): Agency for Healthcare Research and Quality; 2002 Oct. Electronic copies: Available from USPSTF Web site.

PATIENT RESOURCES

The following is available:

- The Pocket Guide to Good Health for Adults. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2003.

Electronic copies: Available from the U.S. Preventive Services Task Force (USPSTF) Web site. Copies also available in Spanish from the USPSTF Web site.

Print copies: Available from the Agency for Healthcare Research and Quality (AHRQ) Publications Clearinghouse. For more information, go to http://www.ahrq.gov/news/pubsix.htm or call 1-800-358-9295 (U.S. only).

NGC STATUS

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